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Review article

A review of the reproductive consequences of consanguinity

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ABSTRACT

Background: Consanguinity is the close union, sexual relationship or marriage between persons who have common biological ancestors usually up to about 2nd cousins. Contrary to general opinion consanguinity is quite common and is practiced worldwide. It is an important topic as while rates of consanguineous unions in certain society have decreased over time, rates have remained stable or increased in other societies with rates as high as 80.6% in some communities. Our aim was to conduct a review looking at general aspects of consanguinity and any published reproductive outcomes in literature. We also looked at possible future directions that could be relevant in the management of the consanguineous couple to help improve reproductive outcomes.

Method: We conducted a PUBMED, CINAHL, Web of Knowledge and Google Scholar search looking at articles on consanguinity. Consanguinity articles related to pregnancy and reproduction were searched using additional filters looking at our specific areas of interest. All relevant publications up to March 2015 were reviewed. Additional search for relevant articles pertaining to pre implantation genetic diagnosis for future directions in the management of the consanguineous couple was done. Most publications were found in books, on line articles and journals. Most were retrospective, population or cohort studies.

Result: Consanguinity is practiced by up to 10% of the world's population with rates ranging from 80.6% in certain provinces in the Middle East to less than 1% in western societies. It predates Islam and has been practiced since Old Testament times. The most commonly cited reason for consanguinity is sociocultural and socioeconomic although it is also more common in certain religions. In areas where rates of Consanguinity are reducing urban migration and increasing education rates are thought to be contributory.

Congenital malformations have long been established to be higher in consanguineous couples above the background rate (4.5% Vs 1%). Due to "Founder effect" or a common ancestor, Consanguinity is most commonly associated with Inborn errors of metabolism most of which are autosomal recessive.

Consanguinity increases the incidence of multifactorial disorders such as diabetes, cardiovascular disorders, obesity and certain types of cancers. These may in turn affect reproductive outcomes. It may also affect fertility rates. Pregnancy outcomes like increased pregnancy wastages and preterm labor have been reported with consanguinity. Other studies produced conflicting evidence on its effect regarding outcomes like hypertensive disorders of pregnancy and Intrauterine growth restriction.

Conclusion: Consanguinity continues to be practiced worldwide and in some countries rates are increasing. The main reason for the practice appears to be sociocultural and socioeconomic although religious beliefs is a contributory factor. The most significant effects on reproductive outcomes are mostly due to autosomal recessive inherited conditions and inborn errors of metabolism. It also significantly increases the inheritance of certain multifactorial disorders like diabetes which may indirectly affect reproductive outcomes. In the future with the completion of the study of the whole human Genome and current advances in Pre implantation Genetic diagnosis and screening it may be possible to mitigate some of the adverse reproductive outcomes associated with consanguinity.

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Introduction

Consanguinity is important because of its possible effects on reproductive outcomes. It is a fascinating and often debated subject not in the least because of the salacious interest and moral stance sometimes adopted towards it by cultures that do not practice consanguinity. Charles Darwin in the mid-19th century in England was one of the first scientifically minded writers to examine the issue of consanguinity and explore some of the reproductive consequences. At the time Charles himself was married to his first cousin [1].

There are cultural, social and clinical implications for couples in such unions. Due to the sharing of common alleles, it may lead to several reproductive consequences both in the mother and the offspring. This in turn may have a deleterious effect on reproduction, the family and society as a whole.

This review examines currently available evidence on general aspects of consanguinity with emphasis on reproductive consequences.

Definition

The dictionary definition of Consanguinity dates from around the 14th century BC, however, the practice itself has been known since biblical times. Consanguinity is derived from the French word “consanguinité” and from the Latin word “consanguinitatem” meaning “of the same blood,” or being descended from the same ancestor as another person [2].

The modern day definition of Consanguinity is close union, sexual relations or marriage between persons who have common biological ancestors usually up to 2nd cousins. This definition of the degree of relatedness between couples has been chosen because the genetic influence in marriages between couples related to a lesser degree would be expected to differ only slightly from that observed in the general population [3].

Incidence

Contrary to general opinion consanguineous unions are quite common. It is thought that up to 500–800 million people globally or 10% of the world’s population are of consanguineous parentage. Fig. 1 shows a schematic representation of consanguineous marriage rates worldwide. Only second-cousin and closer marriages are represented [4].

Western countries tend to have low rates of consanguinity apart from within local immigrant populations (such as the Pakistani Muslim community in the Northwest of England). The highest rates are seen in countries like Qatar (54%) [5], Saudi Arabia, 56% [6], Pakistan, up to 57% and some South Indian urban communities [7]. The highest quoted consanguinity rates in the literature are 76% reported in certain Pakistani Army communities [8] and 80.6% in the Samtah province of Saudi Arabia [9]. Rates are also higher in some parts of Africa and Pacific Asia (20–55%) [10].

While current rates are generally low in Western countries, the practice of consanguinity is well recorded in areas where it has been practiced for centuries. Table 1 summarizes the rates as reported by various authors.

There is evidence that while the prevalence of consanguinity may be increasing in some communities [11–13], the incidence has been noted to have decreased over time in others [13]. In a study by Zlotogora et al in a predominantly Muslim Israeli village, the incidence was found to have reduced to 20% over a 20 year period [14]. In the Kamma community of Andhra Pradesh India, there has been gradual decline over the last 40 years thought to mostly be due to the decline in uncle-niece marriages and the reduction in the number of children per marriage. This has resulted in a reduction in the number of eligible cousins for the marriage mat [15]. The trend in countries like Bahrain [16], Jordan [17], Turkey [18] Brazil [19] and Japan [20] has been downwards over time while in countries like Oman rates have remained stable [21].

In previous population studies, the highest rates of consanguineous marriages were associated with low socioeconomic status, illiteracy, and rural populations [22,23] however this may no longer be the case. For example a high prevalence of marital unions between close relatives of land-owning families has been reported in urban areas in India [24], as well as in traditional ruling groups and higher socioeconomic classes by Al Thakeb, 1985. In the Gulf Region the rates are higher in more affluent families as they strive to protect or enhance their wealth and to keep it within the family.

Types

Globally, the most common form of consanguinity is between first cousins. First cousin spouses share 1/8 of inherited genes from a common ancestor, and so their progeny or children are homozygous at 1/16 of all loci. Conventionally this is expressed as the coefficient of inbreeding (F) and for first cousin offspring $F=0.0625$. [25] This is illustrated in Figs. 2 and 3.

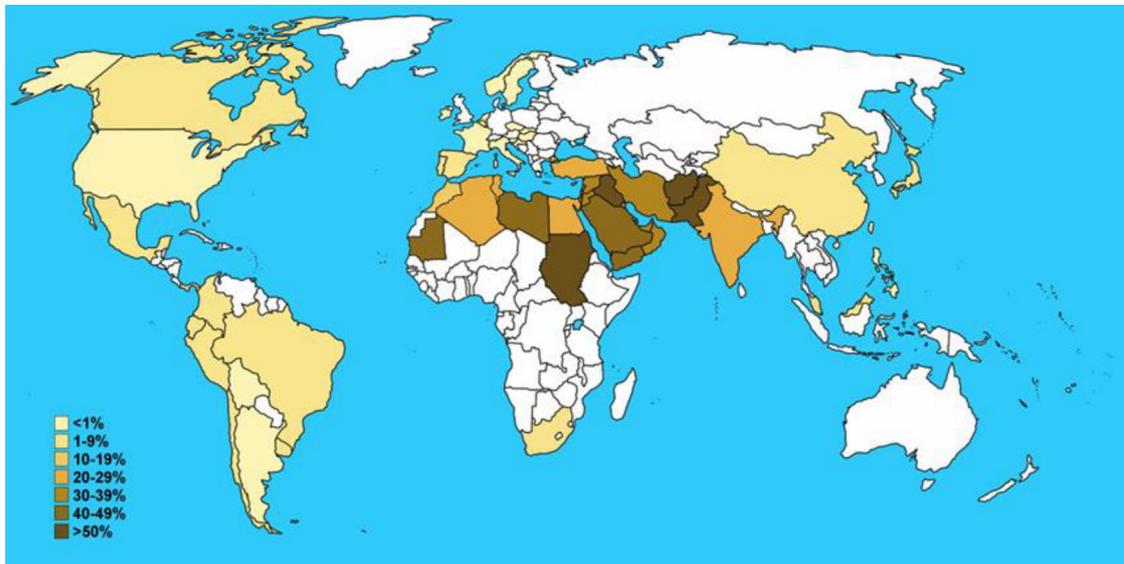


Fig. 1. Schematic representation of consanguineous marriage rates worldwide. Only second-cousin and closer marriages are represented. Adapted from Tadmouri et al. Reproductive Health 2009.

Consanguineous unions could be between first, second and third cousins, as well as double 1st cousins or double 2nd cousins. Maternal uncle-niece marriage [26] and aunt-nephew unions are also practiced in some Hindu populations of South India [27]. Table 2 shows the various types of consanguineous unions and the relationship between the spouses.

Consanguinity dates as far back as the Ptolemy period in ancient Egypt (305 BC) where half sibling marriages were widely practiced [28]. Official census from Roman Egypt showed that up to 23.0% of all marriages may have been between brothers and sisters [29]. In the West, consanguineous unions were most frequently contracted between the Ruling classes, Royal families or Aristocrats [4] whereas in less resourced countries it is commonest in poor rural communities with low levels of education. Paradoxically in a study in the UAE a country with consanguinity levels of 50.5% it was associated with higher levels of education in the male spouse [30].

Jurdi et al reported the same finding in a 1997 demographic survey in Yemen [31].

Predisposing factors

(a) Religious perspective

Consanguinity has some Religious basis and this is an important factor influencing prevalence in some communities. Certain religions are more favorably disposed to consanguinity. In Judaism and Buddhism consanguineous unions are sanctioned. Attitudes towards consanguinity within Islam are ambiguous, but it is thought that generally Islam favors consanguineous unions [4] seen as following the “Sunnah” or deeds of the prophet. Khoury et al in 1992 found the practice to be more common in those households with Muslim affiliations. [32] Because consanguineous unions predate Islam, some authors believe that it is socio-cultural rather than an Islamic influence [33,34]. Christianity in the past might have been seen as condoning consanguineous unions but by 591 CE a special dispensation had to be obtained from the church to marry a relative closer than a certain degree due to a Papal legislation citing the book of Leviticus [1].

• Social Aspects

The most important reason cited for the preference for cousin unions in most parts of the world appears to be social and cultural [7]. This is especially so in countries like Pakistan and in the Middle East. Other reasons cited include shared religious values and common ethnic, social and tribal traditions between couples. At a family level, consanguineous unions are thought to be stronger at maintaining ties between families leading to greater marriage stability [21] and lower rates of marital disharmony. There is strengthening of family ties and as husband and wife are related, it is thought that the bride would be better treated. There is also better relationships between the bride and her in-laws as the bride is also their relative [35].

Perpetuating factors

In more affluent societies such as oil rich Middle East, the prevalence of consanguineous marriages is either increasing or has

Table 1
The prevalence of consanguinity by country and year of publication Oniya 2017.

Country	Consanguinity rate	Author
1.Kuwait	68.0%	Madi et al. 2006
2.Saudi Arabia	56.0%	El Mouzan et al. 2007
3.Pakistan	55-59%	Shaw et al. 2008
4.Qatar	54.0%	Benner et al. 2004
5.Oman	52%	Islam et al. 2012
6.Jordan	51.2%	Khoury et al. 1992
7.UAE	50.5%	Al gazali et al. 1997
8.Sudan	49.5%	Saha et al. 1990
9.Yemen	40.0%	Jurdi et al. 2003
9. Algeria	40.0%	R Flicek et al. 2006
10.Iran	37.4%	Hosseini et al. 2014
11.Lebanon	35.55%	Barbour et al. 2009
12.Syria	35.4%	Othman et al. 2009
13.Egypt	28.9%	Hafez et al. 1983
14.Israel	24%	Na’amnih et al. 2014
15.Turkey	21.2%	Basaran et al. 1988
16.Sweden	20.8%	Bittles et al. 2005
17.Morocco	15.25%	Jaouad et al. 2009
18.Brazil	5.0%	Freire-Maia et al. 1990
19.Japan	3.9%	Imaizumi et al. 1986
20.Norway	3.7%	Saugstad et al. 1977
21.Hungary	2.9%	Czeizel et al. 1976
22.Uruguay	2.23%	Lusiardo et al. 2004
23.England	<1%	Smith et al. 2001

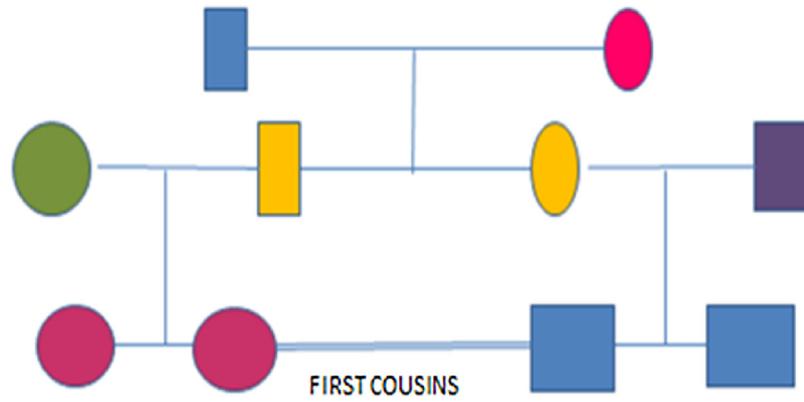


Fig. 2. First cousin Marriage Oniya2017.

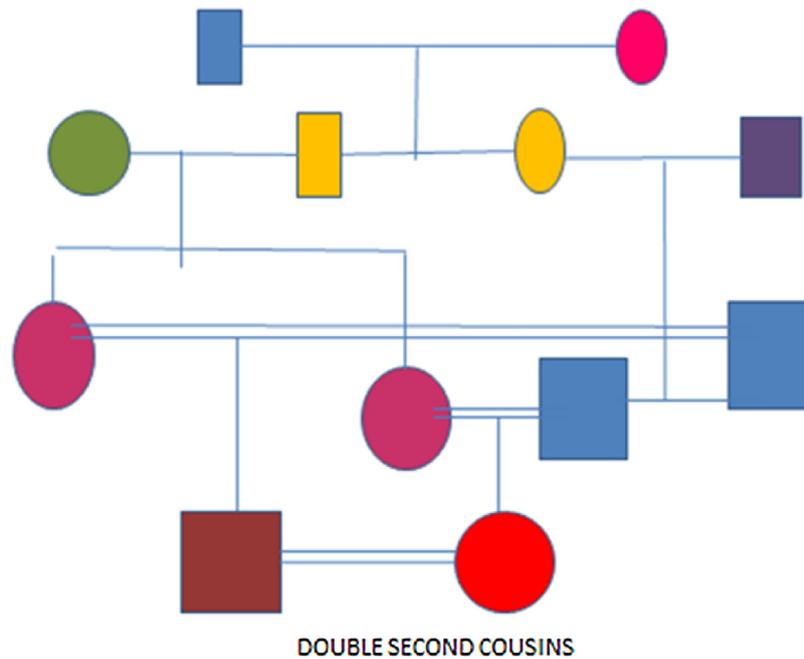


Fig. 3. Double first cousin marriage. Oniya 2017.

Table 2
Types of Consanguineous Unions.

Types of consanguineous Unions	Relationship between consanguineous spouse
First Cousins	Share common Grand parent
First Cousin once removed	Children of first cousins
Double First cousins	Both sets of in laws are first cousins
Second cousins	Share common Great grand parents
Second cousin once removed	Children of second cousins
Double second cousins	Both sets of in laws are second cousins
Uncle - Niece	Uncle and Niece union
Aunt- Nephew	Aunt and Nephew union

stayed the same. This is thought to help preserve wealth in families [36]. In south India, the tradition of marriage dowry payment is less common in consanguineous than in unrelated marriages [37] which has perpetuated the practice.

In small immigrant communities a perpetuating factor for consanguineous unions is the need to marry within the community due to shared moral, social and religious norms. In this instance the consanguinity rate among these communities far

exceeds the background rate of the indigenous population. For example the consanguinity rate in Muslim Pakistanis in Bradford in the North East of England is about 69% [27] as compared to a national rate of less than 1% [38].

In other small isolated rural communities geographical distance and outward migration to urban areas with no influx of potential new genes into marriage pools of the rural areas is a perpetuating factor for consanguineous marriages.

Factors contributing to reducing rates

The disadvantages of consanguineous unions are now generally accepted to be much less than previously thought or at least outweighed by the advantages by most authors [39–41]. Despite this, there is some social stigma attached to consanguinity although this tends to be towards small migrant communities living in Western societies. In countries where highly consanguineous communities are indigenous it is an acceptable social norm.

With increasing levels of education, there is increased awareness that children born within consanguineous unions may be “malformed”. This is further reinforced if there are affected children in the family [18]. This fact may have contributed to decreasing rates of consanguinity in communities where rates are reducing. Other factors contributing to reducing prevalence are increased age at marriage [42] due to higher education levels in females and increasing awareness of the social inappropriateness of wide age gaps between couples. For example there has been a proscription of uncle–niece unions because of wide age gap in Punjabi Muslims in India and this has led to reducing rates of such unions [42]. Consanguineous unions is prohibited in most Hindu communities in Northern and North eastern states in India [43].

In other countries like the United States of America marriage between cousins is banned in most states [44] and can only be performed by special license in some small immigrant groups or under specific circumstances. In Brazil secular and religious laws which apply to the entire country control the degree of consanguinity and forbid marriages between ancestors and descendants, as well as between siblings [19].

Reproductive consequences

Medical disorders

The impact of consanguinity on medical disorders in women is summarized in Table 3. These disorders have either direct or indirect consequences on reproduction.

It has been extensively documented that consanguinity increases the incidence of multifactorial disorders such as diabetes, cardiovascular (CVS) disorders, obesity and certain types of cancers [45] and this may in turn indirectly contribute to adverse reproductive outcomes although other studies disagree with these findings [46].

Consanguinity itself has been implicated in helping to preserve or enhance the survival of genotypes that are protective against malaria [47] such as the Alpha thalassemia trait which has important reproductive consequences as the homozygous state is lethal.

The incidence of other conditions like Asthma, Mental retardation, Epilepsy, Diabetes and Schizophrenia has been found to be increased by consanguinity in some studies [48]. Conversely the incidence of breast cancer is thought to be reduced in offspring of consanguineous unions [49].

Fertility

Some Authors reported lower fertility rates among highly inbred women as evidenced by long inter-birth intervals. [50] Consanguinity is also thought to affect the age at menopause [51] and may be associated with autosomal recessive premature ovarian failure [52]. Other authors reported that there is higher fertility rates and hence bigger family size [42] although it is uncertain whether this is due to early marriages and therefore longer reproductive lives or better maternal fetal compatibility due to more shared gene loci from a consanguineous union [53]. Another theory that has been postulated for increased fertility is reproductive compensation to make up for pregnancy wastages [42]. Contraceptive use has been reported to be less in consanguineous couples [54] and women in such unions have babies for much longer [55], tend to extend child bearing till a late age and have higher numbers of live births and children. In a study of 5515 women in Iran, consanguineous couples had higher mean numbers of pregnancies, live births and surviving children [56]. Some authors, however, found no change in fertility rates [57].

Table 4 summarizes the fertility consequences of consanguinity.

Psychosexual

In 1891 Edward Westermack observed that enhanced fertility in consanguineous couples may be counter balanced by aversion to sex or absence of sexual feelings found in some consanguineous and incestuous unions as couples have often been raised together in the same family leading to sexual aversion. This Westermack effect [58] has also been referred to as “reverse sexual imprinting”. Switching to suddenly becoming sexual partners may be difficult and Sex may for such couples become an activity done simply to procreate [59]. Denic et al also postulated that the Westermack effect may make consanguinity a risk factor for cervical cancer as couples may wish to satisfy sexual desire outside marriage leading to higher rates of HPV carriage [60] and hence cervical cancer.

Pregnancy loss or wastage

Pregnancy wastages from periconceptual losses and miscarriages have been reported by some authors to be slightly more common due to genetic problems [53]. However in a study by Gowri et al consanguinity did not appear to play a significant role in the etiology of recurrent spontaneous miscarriages. [61] Similarly, Saad et al found no association between consanguinity and pregnancy loss, early miscarriages or gestational age at delivery [62].

Pregnancy complications

Studies on the effect of consanguinity on pre-eclampsia are contradictory. Stevenson et al noted that it does not appear to increase the risk of pre-eclampsia or hypertensive disorders in pregnancy and to the contrary may lower the risk [63]. Sezik et al also found that it had no effect on the development of maternal and fetal complications of Pre-eclampsia [64]. Conversely Berends et al

Table 3
Maternal diseases linked to consanguinity.

OUTCOME	AUTHORS	DATE
An increased risk of multi-factorial disorders- such as diabetes, psychosis, obesity, cancers, CVS disease in consanguineous couples.	Bittles et al	2010
Increased incidence of asthma, mental retardation, epilepsy and diabetes	Bener et al (Bener and Hussain, 2006) [88]	2006
Decreased risk of breast cancer	Bener et al (Bener, Al-Kubaisi and Al-Sulaiti, 2010)[88]	2010
Increased risk of Schizophrenia	Bener et al (Bener, Dafeeah and Samson, 2012)	2012
Increased susceptibility to infection	Lyons et al (Lyons, et al., 2009)[89]	2009

Table 4
Summary of the fertility consequences of consanguinity.

OUTCOME	AUTHORS	DATE
Higher fertility rate	Bittles et al (Bittles, Grant, Sullivan and Hussain, 2002) [55]	2002
Higher number of pregnancies	Hussein et al (Hussain and Bittles, 1999) [90]	1999
Lower Fertility	Ober et al 1999 [50]	1999
Less use Contraception/ family planning	Islam et al (Islam, 2013) [54]	2013
Early age at child bearing	Hosseini-chavoshi et al(Hosseini-Chavoshi, Abbasi-Shavazi and Bittles, 2014) [56]	2014
Longer reproductive life	Bittles et al (Bittles, Grant, Sullivan and Hussain, 2002) [55]	2001
Higher number of livebirths	Hosseini-chavoshi et al (Hosseini-Chavoshi, Abbasi-Shavazi and Bittles, 2014) [56]	2014
	Bener et al (Bener and Hussain, 2006) [88]	2006
Lower fertility rates	Hussein et al (Hussain and Bittles, 2004) [91]	2004
Periconceptual losses	Hussein et al(Hussain and Bittles, 1999) [90]	1999
Autosomal recessive premature ovarian failure	Caburet et al (Caburet, Zavadakova, Ben-Neriah, Bouhali, Dipietromaria, Charon, 2012) [52]	2012

Table 5
Early and late Pregnancy complications associated with consanguinity.

OUTCOME	AUTHORS	DATE
No association with Hyperemesis.Preterm labour less than 33 weeks	Grjibovski et al (Grjibovski et al 2008 [92] Mumtaz et al (Mumtaz, Nassar, Mahfoud, El-Khamra, Al-Choueiri, Adra, Murray, Zalloua and Yunis, 2010)[67]	2010
Increased incidence of pre-eclampsia	Anvar et al (Anvar, et al., 2011) [93]	2011
Reduced incidence of Preeclampsia	Stevenson et al (Stevenson, Say, Ustaoglu and Durmus, 1976) [63]	
Lower rates of Rhesus incompatibility	Bittles et al (Bittles and Black, 2010) [53]	2010
Preterm delivery	Obeidat et al (Obeidat, Khader, Amarin, Kassawneh and Al Omari, 2010) [71]	2010
Lower birth weight	Jaber et al (Jaber, et al., 1997) [94]	1997

found consanguinity to be positively associated with Pre-eclampsia and fetal growth restriction [65] and even suggested a common etiology, caused by a recessive mutation. Other authors have found no association between consanguinity and the incidence of Pre-eclampsia and Eclampsia [66].

Some studies have shown consanguinity to be associated with an increased risk of spontaneous preterm delivery at less than 33 weeks [67] but not with preterm delivery between 36 and 37 weeks.

Table 5 summarizes pregnancy complications linked with consanguinity and studies reporting these.

Congenital malformations

Several studies showed that the rate of congenital malformations among the offspring of consanguineous marriages is approximately 2.5 times higher than among the offspring of unrelated parents. [39,68,69] In the Bradford study by Sheridan

Table 6
Fetal consequences of Consanguinity.

OUTCOME	AUTHORS	DATE
Congenital malformations	Sogaard et al (Sogaard and Vedsted-Jakobsen, 2003) [96]	2003
	Madi et al (Madi, Al-Naggar, Al-Awadi and Bastaki, 2005) [72]	2005
In born errors of metabolism	Hutchesson et al 7[116]	1998
Decreased birth weight	Magnus P et al (Magnus, Berg and Bjerkedal, 1985) [95]	1985
Intra Uterine Growth Restriction	Al-Eissa et al (al-Eissa, et al., 1995) [97]	1995
Decreased birth weight for gestational weight	Mumtaz G et al (Mumtaz, Tamim, Kanaan, Khawaja, Khogali 2007) [76]	2007
Increased Postnatal/Neonatal morbidity	Babour et al (Barbour and Salameh, 2009) [98]	2009
Increased Perinatal, Neonatal and infant deaths. Increased infant and childhood mortality	Wong et al (Wong and Anokute, 1990) [99] Grant et al 1997 [87]	1990
Death in previous sibling	Bromiker et al (Bromiker, et al., 2004) [100]	2004
No effect on birthweight	Al-Abdulkareem (al-Abdulkareem and Ballal, 1998) [40]	1998
Higher incidences of illnesses	Abdulrazzaq et al (Abdulrazzaq, et al., 1997) [101]	1997
Higher Syndromal and Multiple abnormalities	Al-Gazali et al (al-Gazali, et al., 1995) [102]	1995
Autosomal Recessive disorders	Bundey et al (Bundey, Alam, Kaur, Mir and Lancashire, 1991) [75]	1991
	Jaouad et al (Jaouad, et al.) [103]	2009
Increased Major Malformations	Jabber et al (Jaber, Merlob, Bu, Rotter and Shohat, 1992) [68]	1992
Meckels syndrome	Crawfurd et al (Crawfurd Md, et al., 1978) [105]	1978
Congenital heart disease (ASD, VSD, AVSD, PA,PS)	Becker et al (Becker, et al., 2001) [106]	2001
	Yunis et al (Yunis, et al., 2006) [107]	2006
Neural tube defects	Zlotogora et al (Zlotogora, 1997) [108]	1997
Mental retardation, physical retardation, bilateral cleft lip /cleft palate, cystic fibrosis, and congenital blindness.	Kannan et al [115]	2008
Progeroid Syndrome	Akawi et al (Akawi, et al., 2013) [109]	2013
CNS anomalies AR, Cerebral Palsy	Al Gazali et al (Al-Gazali, et al., 1999) [110] Sinha et al (Sinha et al 1997) [104]	1999
Developmental Delay	Masri et al (Masri, et al., 2011) [111]	2011
?Cardiac issues/ cardiomyopathies	Stollberger et al (Stollberger and Finsterer, 2007) [112]	2007
Male infertility	Kobeissi et al (Kobeissi and Inhorn, 2007) [113]	2007
	Inhorn et al(Inhorn, et al., 2009) [114]	2009

et al consanguinity was associated with a doubling of risk for congenital anomaly [70]. The risk in first cousin parents is variously quoted as around 4.5% [69,71]. In a retrospective study of 7739 births in Kuwait with a consanguinity is rate of 68%, the congenital anomaly rate was found to be 12.5%. Genetic factors were implicated in 79% of cases [72].

Due to "Founder effect" or a common ancestor, Consanguinity is most commonly associated with inborn errors of metabolism due to high carriage of founder recessive genes. The founder effect is seen when a new colony is started by a small number of people from an original population as sometimes seen in small migrant communities. This leads to loss of genetic variation especially if consanguineous marriage is practiced as the agene pool is limited to that of the few original founding member. This leads to an increased rate of autosomal recessive disorders in the children of consanguineous couples [73].

It has been suggest that some of the initially reported significantly elevated levels of fetal malformations previously seen in the children born in highly consanguineous populations may not be due solely to consanguinity but may be multifactorial. For instance high rates of congenital cataract and deafness seen in the Pakistani community in the United Kingdom which originally had been attributed to high consanguinity rates is now thought to be partly due to high CMV carrier rates. [74] Bundey S et al also concluded that the excess of cardiac malformations found in these babies could not be attributed solely to consanguinity [75].

Other fetal complications include lower weight for gestational age [76,77] and low birth weight (OR 1.9) [78,79] as shown in Table 6.

Genetic

The common progenitor in highly consanguineous communities may pass on single gene defects. Due to lack of new healthier gene pool influx, this leads to an increased incidence of single gene defects and inborn errors of metabolism in descendants. This may in turn lead to fetal malformations and more pregnancy wastages. There is a significantly higher incidence of inborn errors of

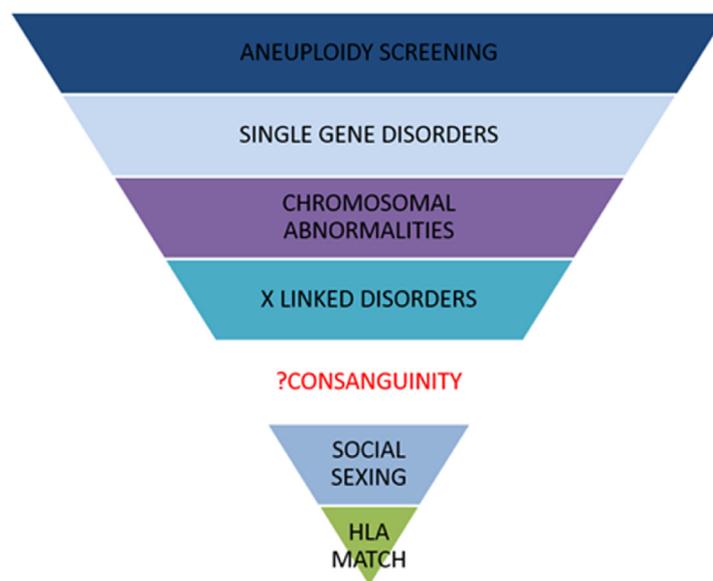
metabolism in children born to consanguineous couples presumably because most of these conditions have an autosomal recessive pattern of inheritance [80,81]. In a study of in-born errors of metabolism (IEM) in Oman, 95% of such children were born to second cousins or closer relatives who were couples [82].

There are several reported series/cases of new inborn errors of metabolism, malformation sequences and congenital anomalies associated with consanguinity but these are typically isolated case reports, retrospective studies and surveys. Comprehensive Literature is lacking. In countries that have invested in genetic studies and genomic surveys it is hoped that these will shed more light in future.

Future directions

With the completion of the study of the whole human Genome and continuing study in this area to further understand what the vast array of genes in the human body may represent, it may be possible to start collecting statistically significant prospective data in consanguineous populations. This may in turn help with Preimplantation genetic diagnosis meaning that the marked increase in the incidence of single gene disorders in children of consanguineous may become a thing of the past as we are able to map the whole genetic array. Faulty ancestral genes can then be avoided using assisted reproduction techniques [83]. Therefore the role of Clinical Genetics in the field of pre-implantation genetic diagnosis (PGD) and Preimplantation genetic screening (PGS) in the diagnosis of preexisting single gene malformations and new de novo genetic mutations cannot be under estimated in the future in helping to improve the reproductive outcomes and in preventing pregnancy wastages in the consanguineous couple.

Traditionally prenatal diagnosis has relied heavily on antenatal screening and invasive testing such as Nuchal translucency measurements combined with biomarker assays in early pregnancy. Very recently non-invasive prenatal testing (NIPT) and invasive testing such as chorionic villous sampling and amniocentesis are used to diagnose the presence of single gene or chromosomal disorders using polymerase chain reaction (PCR) and fluorescent in situ Hybridization techniques (FISH). Diagnosis, however is only



Indications for Preimplantation genetic diagnosis. Oniya et al 2015

Fig. 4. Inverted pyramid showing the most common current indications for PGD.

possible after conception has already occurred and in the case of an affected fetus the only option left for the consanguineous couple is termination of pregnancy or to continue with the pregnancy and birth of a disabled child. This option is sometimes unacceptable due to cultural sensitivity or religious reasons especially in the communities where consanguinity is frequently practiced.

With the advent of PGD and PGS a consanguineous couple who are known to carry a genetic mutation can have procedures such as single cell genomics [83]. In Vitro fertilization (IVF) is used to select embryos that are unaffected by any known defect for transfer during IVF cycles [84]. As technology advances, there invariably will be an expansion in the number of techniques available for PGD as well as the spectrum of conditions that can be diagnosed as this is a rapidly evolving field.

Fig. 4 is an inverted pyramid showing the most common current indications for PGD. There is a potential role for Preimplantation Genetic Diagnosis in diagnosing properly mapped genetic disorders in consanguineous couples. Identifying such linkages and preventing them is a challenge of the future. It is possible in the future that in well-resourced settings consanguinity could become an indication for PGD.

Conclusion

Consanguinity is practiced worldwide and in some communities the incidence may be increasing while in others especially where there has been effective genetic counselling programs it is reducing. Various factors have contributed to the ongoing practice but the most commonly cited are cultural, religious and socio economic. There is increasing awareness of possible adverse reproductive consequences of consanguineous unions and in many highly consanguineous societies there are public health campaigns to address this and in some instances government legislation to raise awareness and provide counselling. In countries where this has been successful consanguinity rates have been falling [85,86].

Various studies on consanguinity have been conducted, most are retrospective and cohort studies looking at various reproductive outcomes in the consanguineous couple. Reproductive advantages of consanguinity appears to be numerous. They include early age at child bearing, longer reproductive life, higher number of life births and possibly increased fertility. Social advantages include more harmonious and stable unions, shared religious, cultural and social norms and preservation of family wealth and identity.

The main reproductive disadvantages of Consanguinity appear to be increased risk of multifactorial disorders like Diabetes, Cardiovascular disorders, Obesity and certain types of cancers which may indirectly affect reproduction.

The rate of congenital malformations is reported to be increased or doubled in consanguineous compared to unrelated couples. Rates of Inborn errors of Metabolism are higher as most are autosomal recessive and this may in turn lead to pregnancy wastages. For other reproductive outcomes like Preeclampsia, Hypertensive disorders in pregnancy, fetal growth restriction, Preterm delivery and low birth weight the evidence is conflicting.

Other possible reproductive outcomes associated with consanguinity include premature ovarian failure and possible Sexual aversion.

With the advent of whole genome mapping as well as further advances with PGD and PGS, in vitro fertilization techniques where available may allow the consanguineous couple to improve their reproductive outcomes in terms of genetic abnormalities which in turn may prevent some of the pregnancy, fetal and other reproductive disadvantages of consanguinity.

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